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Health and Environmental Effects Profile for Methylhydrazine

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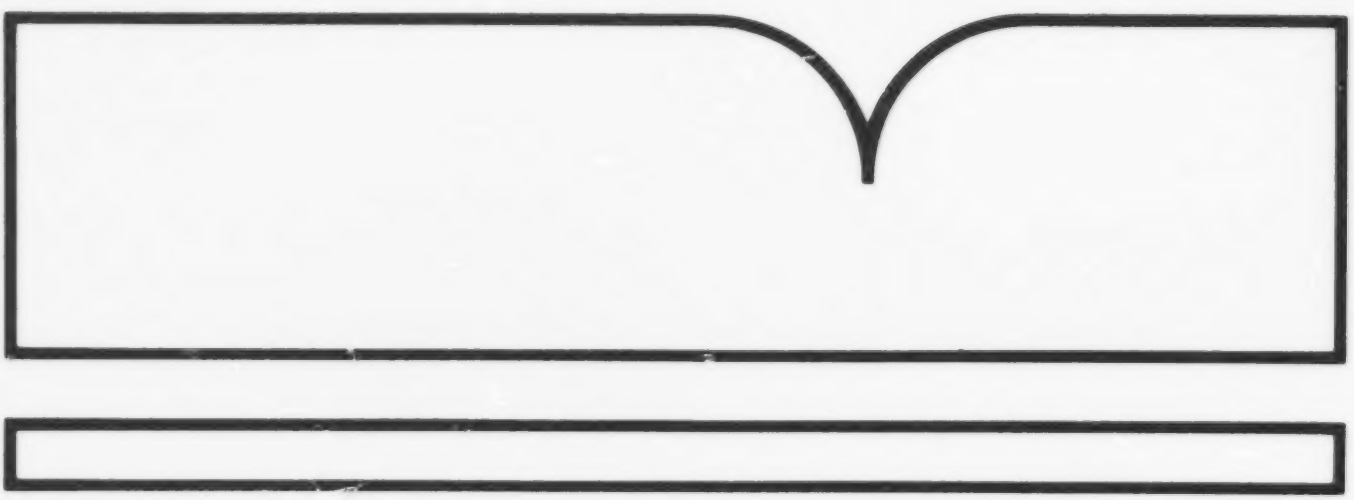

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR METHYLHYDRAZINE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for methylhydrazine was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Methylhydrazine has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for methylhydrazine is 1.1 (mg/kg bw/day)$^{-1}$ for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
TLV	Threshold limit value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Methylhydrazine is also known as monomethylhydrazine. The structure of methylhydrazine is given below:

$$CH_3 - NH - NH_2$$

Molecular Fomula: CH_6N_2

Molecular Weight: 46.1

The Chemical Abstract Service (CAS) Registry Number for methylhydrazine is 6034-4.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Methylhydrazine is a colorless flammable liquid at ambient temperature that can absorb carbon dioxide and water from the air (NIOSH, 1978). It has an ammonia-like fishy smell that is characteristic of alkyl hydrazines. Some of the physical and chemical properties of methylhydrazine are summarized below (NIOSH, 1978, unless otherwise stated):

Boiling point:	87.5°C
Freezing point:	-52.4°C (Hawley, 1981)
Density (at 20°C):	0.874
Vapor pressure:	49.6 mm Hg at 25°C
Solubility:	miscible with water
Chemical reactivity:	highly reactive; it is easily oxidizable

1.3. PRODUCTION DATA

The 1977 TSCA production file lists production of methylhydrazine as 100,000-1,000,000 pounds/year by the Olin Corporation. NIOSH (1978) reported that ~200,000 pounds of methylhydrazine are produced annually in the United States. Methylhydrazine is made commercially by a modified Raschig synthesis, in which chloramine is reacted with methylamine (Schiessl, 1980).

1.4. USE DATA

Methylhydrazine, alone or in combination with hydrazine and/or 1,1-dimethylhydrazine, is used primarily as a high-energy fuel in military applications (e.g., rocket propellants and fuels for thrusters and small electrical power generating units) (Tuazon et al., 1982). The Space Shuttle system, for example, currently employs these fuels in large quantities.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Methylhydrazine can be released to the atmosphere during use (e.g. residual rocket fuel), and from spills, leaks and venting during loading, transfer and storage. It appears that reaction with ozone and hydroxyl radicals will be the major fate of methylhydrazine in the atmosphere. Methylhydrazine does not photolyze in the solar actinic region (λ >290 nm) (Tuazon et al., 1981).

Studies in which 1-20 ppm concentrations of methylhydrazine were mixed with similar levels of ozone under dark conditions (i.e. in a 30,000 ℓ outdoor and ~6400 ℓ or ~3800 ℓ indoor Teflon chambers) showed that the reaction was complete in <2-3 minutes (Tuazon et al., 1981, 1982). The mixture of reaction products depended upon whether excess O_3 or excess methylhydrazine was present; the major products were methyl hydroperoxide (CH_3OOH), methyldiazene (CH_3NNH), diazomethane (CH_2N_2), formaldehyde (HCHO), hydrogen peroxide (H_2O_2) and methanol (CH_3OH). In the presence of excess O_3, CH_3NNH and CH_2N_2 were not seen, but were replaced by higher yields of CH_3OOH, CH_3OH and HCHO (Tuazon et al., 1981).

When 3.2 ppm of methylhydrazine was mixed with dry air (4% relative humidity) under dark conditions without ozone in a large outdoor chamber (30,000 ℓ), the approximate half-life was 4.2 hours. A faster half-life of ~3 hours was observed when air with a higher humidity was used. In similar dark decay experiments with higher levels of methylhydrazine (~10 ppm), half-lives in dry air of 49.8±2.8 hours (10% RH) in a 6400 ℓ indoor chamber and 30.1±0.7 hours (17% RH) in a 3800 ℓ indoor chamber were reported (Tuazon et al., 1982); the half-life in the 3800 ℓ chamber with

air at 60% RH was 19.8±2.3 hours. The reason for the apparent influence of humidity on rate of reaction in the above studies is not known, but it was suggested that the significantly lower dark decay rates in the study that used the 30,000 ℓ outdoor chamber may be related to particulate contamination (e.g., ambient dusts and aerosols, since the chamber was routinely flushed with ambient air prior to filling with purified air). In both of the above studies, NH_3 formed from the autoxidation of methylhydrazine. In a study with the 30,000 ℓ chamber and dry air, NH_3 accounted for as much as 50% of the methylhydrazine that disappeared during the first few minutes, and 20% of the methylhydrazine that disappeared by the half-life; the corresponding values observed for NH_3 formation in humidified air were only ~1/3 that observed in dry air. Methyldiazene (CH_3NNH) and nitrous acid were detected as minor autoxidation products of methylhydrazine, but other products were not detected by infrared spectroscopy (Tuazon et al., 1981, 1982).

It also appears that methylhydrazine can be consumed rapidly by hydroxyl radicals in the atmosphere (Pitts et al., 1981). From data that was obtained under simulated atmospheric conditions in a 30,000 ℓ outdoor Teflon chamber, a rate constant was determined that was independent of temperature and allowed calculation of a tropospheric half-life of ~3 hours. It was further estimated that the half-life would be <1 hour in polluted urban atmospheres.

Tuazon et al. (1982) also found that methylhydrazine reacted at a significant rate with NO_2 in the dark, but only negligibly with NO, unless NO_2 was also present. When excess methylhydrazine and NO_2 were mixed, the reactions were completed in ~60-90 minutes. The reaction of methylhydrazine and NO_2 resulted in the formation of nitrous acid (in high

yields), monomethylhydrazinium nitrate, methyldiazene and methylhydroperoxide (in excess methylhydrazine only), as well as traces of methanol, NO_2 and NH_3. In addition, two unidentified products were formed, probably in significant yields).

Methylhydrazine (~3 ppm) reacted with nitric acid (~7 ppm) in the gas phase in the 3800/6400 ℓ chambers to form methylhydrazinium nitrate at a rate that was too fast for measurement by infrared spectroscopy, but no evidence was obtained for a similar reaction between nitrous acid and methylhydrazine (Tuazon et al., 1982).

2.2. WATER

Banerjee et al. (1981) examined the kinetics of oxidation of methylhydrazine by dissolved oxygen in distilled water as a function of catalyst (cupric ion) concentration. It was found that the oxidation rate comprises a Cu^{+2} catalyzed as well as an uncatalyzed step, and that Cu^{+2} catalysis is important only at Cu^{+2} concentrations $>1x10^{-6}$ M (~63.5 ppb). It was noted that the transition metal ion content in most natural waters is well below this level, indicating that the uncatalyzed reaction rate will be important in determining the persistence of methylhydrazine. From the reported oxidation rate constant for the uncatalyzed reaction, a half-life of ~17 hours at pH 7 can be calculated. It was also suggested that the oxidation of methylhydrazine will be faster at higher pH and slower at lower pH. If the catalytic coefficients of other transition metals approximate that of Cu^{+2}, it can be inferred that the catalytic decomposition of methylhydrazine will be important only if the total metal ion concentration exceeds $1x10^{-6}$ M.

Information on oxidation reactions with free radicals in water, particularly peroxy radicals, was not found in the literature searched (Appendix A). Photolysis (see Section 2.1.) and hydrolysis are not expected to contribute significantly to the environmental fate of methylhydrazine.

The half-life of methylhydrazine in aquatic media was also studied by Braun and Zirrolli (1983). In the absence of microbial degradation and losses due to physical transport processes, the half-life of methylhydrazine, presumably due to chemical reactions with O_2 and other free radicals, was reported to be 10-14 days in ponds and seawaters. The compound was found to be quite stable in distilled water, with <20% decomposition taking place in 12.5 days. However, the pH of the water was not reported, nor was the effect of pH on the decomposition rate studied by these investigators.

The biodegradation of methylhydrazine by four cultures of microorganisms ubiquitous in ambient aquatic environments was studied by Kane and Williamson (1983). These included a mixed culture of nitrifying bacteria (Nitrosomonas Nitrobacter), a single culture of a nitrifying bacteria (Nitrobacter), denitrifying bacteria and anaerobic bacteria. When tested aerobically without added nutrients, it was found that methylhydrazine (50 mg/ℓ) degraded ~30% in 7 days; with typical nutrients added (NH_{4+}, NO_2-, NO_3-, PO_4-3, HCO_3-) the aerobic degradation after 7 days was ~40%. The loss of methylhydrazine during a 6-day bioassay with the anaerobic bacteria was reportedly 26%. Toxic levels of methylhydrazine, defined as the concentration required to reduce substrate metabolism by 50%, were estimated to be 1.4, 14.6, 4.3 and 36 mg/ℓ for the Nitrosomonas Nitrobacter, Nitrobacter, denitrifying and anaerobic bacteria, respectively. [For the Nitrosomonas Nitrobacter and Nitrobacter populations, removal of NH_{4+}-N and NO_{2-}-N,

respectively, were assayed; for the denitrifying and anaerobic bacteria, substrate removal was defined in terms of gas production (nitrogen and methane/CO_2, respectively).] The slow degradation and high toxicity of methylhydrazine, even at low concentrations, indicate that biodegradation may not be a significant process for this compound in aquatic media.

The significance of evaporation as a transport mechanism for methylhydrazine in aquatic media was studied by a few investigators. A measured evaporation rate for methylhydrazine from aqueous solution in Petri dishes under conditions of controlled temperature (21°C) and air velocity (63.5 cm/sec) has been reported to be 1.7 mg/cm² min (MacNaughton et al., 1979). The significance of this value to actual environmental conditions is unclear since the concentration of test solutions was not stated and the simulation did not adequately represent other parameters such as water depth. It should be noted, however, that the evaporation rate for methylhydrazine was found to be 10-fold greater than that determined for unsubstituted hydrazine (0.49 mg/cm² min). Stauffer (1977) has reported that a 25% aqueous solution of unsubstituted hydrazine under the same conditions in Petri plates lost ~8% due to evaporation in the first 6 hours and ~21% in the following 4.8 days. Other experiments with unsubstituted hydrazine indicated that evaporation increases at higher concentrations and in the presence of sunshine (due to thermal rather than photochemical effects). Evaporation may be minimal at ppm concentrations due to the miscibility of methylhydrazine, but experimental data at low concentrations are not available.

2.3. SOIL

The fate and transport of methylhydrazine in soil has not been investigated. Data summarized in Sections 2.1. and 2.2. indicate that this compound released to the soil would be oxidized rapidly by gaseous oxygen or

oxygen that is dissolved in soil water. In areas of high concentrations, as in the case of spills, the ready solubility of methylhydrazine in water suggests that leaching of unevaporated compound could occur.

The adsorption and leaching characteristics of methylhydrazine in different soils was studied by Braun and Zirrolli (1983). These investigators used pure sand (100% sand), two natural soils, and a 1:9 mixture of a natural clay soil and sand for these experiments. In pure sand, no adsorption of methylhydrazine was observed and ~87% of the compound could be leached with water from a 20 cm column. In the three other soils, the adsorption of methylhydrazine varied from 46-73%. Of these total amounts of adsorbed methylhydrazine, 5-20% remained unrecovered (after elution with 0.1 N HCl), presumably due to reactive processes in the soil. The leaching of methylhydrazine with water from the three soils varied from 5.5-6.5%. No discernible correlation between leachability and the soil organic content could be found.

It is evident from the above discussion that methylhydrazine may undergo substantial reactions in soils, and some leaching of this compound from soil to groundwater is possible. However, the correlation between these behaviors and the particular soil characteristics have not been firmly established.

3. EXPOSURE

Monitoring data for methylhydrazine in air, water or food were not found in STORET or in the available literature. The high reactivity of methylhydrazine indicates that this compound will be degraded rapidly in the environment via chemical pathways and that ambient exposure will be negligible. The potential for human exposure does exist, however, during the manufacture, transportation and use of this chemical as a rocket fuel.

4. PHARMACOKINETICS

The pharmacokinetics of methylhydrazine have not been fully characterized. Several studies have attempted to elucidate the complex mechanisms by which methylhydrazine exerts its effects and is removed from the body.

4.1. ABSORPTION

No specific information was encountered, but absorption of methylhydrazine has been reported to occur via inhalation or ingestion (Rheinhardt and Britelli, 1981).

Smith and Clark (1969) investigated the effects of percutaneous administration of methylhydrazine in 16 dogs. Male mongrel dogs, anesthetized with pentobarbital, received a methylhydrazine application of 0.32-5.75 mmoles/kg on their shaved chests (300 cm^2 area). Blood samples for determining methemoglobin and plasma methylhydrazine concentrations were taken at various intervals from a catheter placed in the femoral artery. Physiological saline was used to compensate for the volumes of blood removed. Samples were removed within the first minute and every 10 minutes for the first hour, then every 60 minutes until 360 minutes post-administration.

Methylhydrazine was rapidly absorbed; it was detected in the blood 30 seconds after administration. Plasma levels reached a peak 60 minutes after administration and remained relatively constant. Plasma methemoglobin levels quickly rose (3-5 minutes) to their maximum values ~120 minutes after application. Unlike plasma methylhydrazine, plasma methemoglobin concentrations declined after reaching a maximum. Treated skin became discolored, swollen and developed marked edema. Convulsions and clonic seizures were observed when the plasma methylhydrazine levels reached ~10 µg/mℓ. An LD_{50} could not be derived because only 1/16 dogs died after treatment.

4.2. DISTRIBUTION

Pinkerton et al. (1967) studied the distribution of ^{14}C-methylhydrazine given by i.p. injection to rats, mice, dogs and monkeys. Groups of 4-5 Sprague-Dawley rats, Swiss mice, mongrel dogs and Macaca mulatta monkeys, equally distributed by sex, received, respectively, i.p. injections of 15, 22, 10 and 10 mg methylhydrazine/kg. Animals were placed in metabolism cages and observed for 2, 4, 8 and 24 hours. Urine was collected, and samples of blood, organs and tissues were removed at necropsy and assayed for radioactivity.

The highest levels of radioactivity were observed in the blood serum, liver, kidney and bladder of all treated animals. Dogs and monkeys had the highest levels in their tissues 4 and 2 hours after administration, respectively. A half-life of ~7 3/4 hours was estimated based on blood radioactivity levels at 4-24 hours after administration.

4.3. METABOLISM

The metabolism of methylhydrazine was discussed in a review by Clark et al. (1968). Several indications of metabolic derangement after methylhydrazine intoxication were discussed, including increased body temperature (Jacobson et al., 1955), hyperglycemia with depletion of liver glycogen (O'Brien et al., 1964; Fortney and Clark, 1967), increased levels of hydrogen peroxide possibly causing lipid peroxidation (Fortney and Clark, 1967), and hemolysis, methemoglobin formation and anemia.

Prough et al. (1969) investigated the in vitro metabolism of methylhydrazine by liver microsomal fractions of Sprague-Dawley rats. Methylhydrazine was metabolized to methane at a rate of 1 m μmole/120 minutes/mg protein in the presence of oxygen and a NADPH generating system. Methylhydrazine can be chemically oxidizing (nonenzymatically) to methane in blood

serum (Prough et al., 1969). An oxidative demethylase system may convert methylhydrazine to carbon dioxide (Dost et al., 1966, 1967).

Methylhydrazine has been reported to undergo oxidation to an azo derivative, which isomerizes to form hydrazone. Hydrogen peroxide is formed during the initial oxidation step, and may account for methylhydrazines cytotoxicity (Berneis et al., 1963).

4.4. EXCRETION

The urinary excretion of methylhydrazine has been investigated in studies comparing it to other weakly basic amines with simple chemical structures, such as ammonia and hydrazine. Hydrazine and methylhydrazine are excreted by the same mechanism, primarily by the kidneys (Clark et al., 1968). Renal reabsorption of monomethylhydrazine was found to be associated with the pH of urine which was varied by sodium bicarbonate infusion. Renal clearance was observed to be ~100% when the urine pH was below 6.5 and ~20% above pH 7 (Coe et al., 1968).

Dost et al. (1966) measured the levels of radioactivity in the urine and expired air of Sprague-Dawley rats for 27 hours after an i.p. injection of 5.5, 11 or 22 mg ^{14}C-methylhydrazine/kg. By 27 hours after injection, 27-34% of the dose was excreted in the expired air. Carbon dioxide accounted for ~20% of this and the remainder was methane. About 41% of the low dose, 40% of the medium dose and 22% of the high dose was excreted in the urine 27 hours after injection. More radioactivity was retained by the rats at the highest dose. The authors believed this indicated that impairment had occurred in the excretion mechanisms.

The distribution study of Pinkerton et al. (1967) demonstrated a species difference in urinary clearance of methylhydrazine. Mice excreted methylhydrazine most rapidly (32.2% in urine after 4 hours), followed by rats

(20.5%) monkeys (16.6%) and dogs (12.6%). Of the dose excreted, ~50% was unchanged methylhydrazine. Dogs were more susceptible to kidney damage by methylhydrazine than the other species tested.

5. EFFECTS

5.1. CARCINOGENCITY

Evidence regarding the carcinogenicity of methylhydrazine in laboratory hamsters and mice has been reported.

Roe et al. (1967) administered 0 or 0.5 mg methylhydrazine sulfate/day by gavage to groups of 25 virgin female Swiss mice, 5 days/week for 40 weeks. Lung tumor incidence in the treated mice was found to be similar to controls.

Kelly et al. (1969) administered 0.46 mg methylhydrazine/day to 30 CDF_1 female mice by gavage and 0.23 mg methylhydrazine/day by i.p. injection to 30 CDF_1 male mice once/week for 8 weeks. Controls consisted of 10 females and 9 males, which received similar treatment with saline solution administered by gavage and i.p. injection, respectively. Histopathological examination revealed that 0/9 surviving gavage-treated mice had pulmonary tumors compared to 1/10 controls. Three out of 30 surviving methylhydrazine injected mice had pulmonary tumors compared to 1/9 control mice. Methylhydrazine did not appear to increase the incidence of pulmonary tumors under these experimental conditions.

MacEwen and Vernot (1975) orally administered methylhydrazine to groups of 30 5-month-old hamsters for their lifetime and observed no significant increases in tumor incidence. Hamsters received freshly prepared 0, 0.01 (buffered, pH 3.5) or 0.01% aqueous solutions of methylhydrazine as their drinking water. Six adrenocortical tumors were observed in 5/25 hamsters receiving methylhydrazine at pH 3.5 compared to 4 tumors in 3/13 controls. Four tumors were observed in 4/25 hamsters receiving unbuffered methylhydrazine. The authors concluded that methylhydrazine was not carcinogenic under the conditions of this study.

Toth (1972) administered methylhydrazine and methylhydrazine sulfate (0.01% and 0.001%, respectively) in the drinking water of groups of 50 male and 50 female 5- to 6-week-old Swiss mice for the remainder of their lifetime, and observed increased incidences of lung adenomas and malignant lymphomas. The average daily intakes of methylhydrazine and methylhydrazine sulfate were based on the observed consumption of water by the mice. Male mice ingested 0.71 and 0.078 mg of methylhydrazine and methylhydrazine sulfate/day, respectively. Female mice ingested 0.66 and 0.102 mg methylhydrazine and methylhydrazine sulfate/day, respectively. Control groups consisted of 110 male and 110 female Swiss mice which received drinking water alone. Upon histopathological examination a variety of tumors were found in treated and control mice. An increased incidence of lung adenomas was observed in mice receiving methylhydrazine sulfate (46/100 compared to 23/100 controls). The lung tumor incidence was 23/100 in mice given methylhydrazine.

The average latency periods of lung tumor appearance for controls, methylhydrazine-treated and methylhydrazine sulfate-treated were 82, 51 and 91 weeks, respectively. Malignant lymphomas were found in 2/50 methylhydrazine-treated females, 10/50 methylhydrazine sulfate-treated females and 16/100 control females. Methylhydrazine sulfate treatment produced more tumors than methylhydrazine at a dose 6-10 times lower. Methylhydrazine appeared to shorten the latency period for lung tumors.

Toth and Shimizu (1973) evaluated the carcinogenicity of freshly prepared aqueous solutions of methylhydrazine in 6-week-old Syrian golden hamsters. Groups of 50 male and 50 female hamsters received 0.01% methylhydrazine in their drinking water (prepared 3 times weekly) for the remainder of their lifetimes. The average daily methylhydrazine intakes were 1.1 and 1.3 mg for the males and females, respectively. Controls consisted of 100

male and 100 female hamsters that received no methylhydrazine in their drinking water. Various tumors were present in the organs and tissues of treated and control hamsters as observed upon macroscopic, light and electron microscopic and histochemical evaluation. Incidences of malignant liver histiocytomas were 16/50 of the treated females, 27/50 of the treated males and 0/200 of the male and female controls. Nine of 50 females and 7/50 males also had tumors of the cecum, compared to 1/100 controls.

The carcinogenicity of methylhydrazine administered to hamsters orally has been demonstrated by Toth and Shimizu (1973).

5.2. MUTAGENICITY

Brusick and Matheson (1976) reported that methylhydrazine (0.0001-5.0 µl/plate) did not induce reverse mutation in Salmonella typhimurium (Strains TA1535, 1537, 1538, 98 and 100), Escherichia coli or Saccharomyces cerevisiae in standard plate tests in the absence or presence of metabolic activation; however, reverse mutation was observed in S. typhimurium TA1535 incubated in the presence of 1 or 5 µl methylhydrazine/ml and rat liver microsomes in a suspension test.

Cultured mouse lymphoma cells and human diploid WI-38 cells gave negative results in a forward mutation assay and in an assay of unscheduled DNA synthesis, respectively (Brusick and Matheson, 1976). Methylhydrazine did not induce dominant lethal mutations in rats or mice (Brusick and Matheson, 1976) given 5 daily i.p. injections of up to 2.6 or 2.5 mg/kg, respectively.

Positive and negative results in more recent mutagenicity assays are summarized in Table 5-1. Methylhydrazine induced reverse mutation in S. typhimurium (von Wright et al., 1978) and E. coli (von Wright and Tikkanen, 1980a,b) in the absence of metabolic activation.

TABLE 5-1

Mutagenicity of Methylhydrazine

Assay	Indicator Organisms	Concentration	Application	Activation[a]	Response[a]	Reference
Reverse mutation (tryp$^+$)	E. coli WP-2	0.5-2.0 µmol/plate	plate incorporation	-	+	von Wright and Tikkanen, 1980a
Reverse mutation (tryp$^+$)	E. coli WP-2	0.5-2.0 µmol/plate	spot test	-	+	von Wright and Tikkanen, 1980a
Reverse mutation (tryp$^+$)	E. coli WP2[b], WP2uvrA[c] or GM87luvrA, recA, lexA[c]	0.5-2.0 µmol/plate	spot test	-	+	von Wright and Tikkanen, 1980b
		0.5 or 1.0 µmol/mℓ	liquid suspension	-	+	
Reverse mutation (his$^+$)	S. typhimurium TA100	2.0-10.0 µmol/disc	spot test	-	±	von Wright et al., 1978
Reverse mutation (his$^+$)	S. typhimurium TA98, TA1950	2.0-10.0 µmol/disc	spot test	-	-	von Wright et al., 1978
Reverse mutation (his$^+$)	S. typhimurium TA100	10-200 µg/plate	plate incorporation	+	-	von Wright et al., 1978
Reverse mutation (his$^+$)	S. typhimurium TA100	1.0-3.0 µmol/plate	plate incorporation	±	-	von Wright and Tikkanen, 1980
Reverse mutation (his$^+$) (host-mediated)	S. typhimurium TA1950	30 mg/kg single oral dose	bacteria injected into mice	NA	-	von Wright et al., 1978
Reverse mutation (his$^+$) (host-mediated)	S. typhimurium TA1950	33 mg/kg, single oral dose	bacteria injected i.p. into mice	NA	-	von Wright and Tikkanen, 1980
Forward mutation (IK, IdR, TG or Ara-C)	mouse lymphoma cells (L5178Y)	0.1-5.0 mM	in vitro culture	-	-	Rogers and Back, 1981

[a]Responses: +, positive; -, negative; -, negative with and without S9 activation system; ±, positive with and negative without S9 activation system

[b]DNA repair-proficient strain

[c]DNA repair-deficient strain

NA - Not applicable

Rogers and Back (1981) reported the absence of mutation in mouse lymphoma cells cultured with up to 5mM methylhydrazine. Host mediated assays using mice and S. typhimurium also have failed to demonstrate the mutagenicity of methylhydrazine (von Wright et al., 1978; von Wright and Tikkanen, 1980a).

5.3. TERATOGENICITY

Evidence of methylhydrazine teratogenicity has been demonstrated in toads but not rodents. Pregnant rats given various doses (unstated) of methylhydrazine sulfate in a single i.p. injection on the 12th day of gestation produced no abnormal offspring (Chaube and Murphy, 1969). South African clawed toad embryos cultured in 3, 5, 10 or 15 mg methylhydrazine/ℓ developed dose-related malfunctions (Greenhouse, 1976).

5.4. OTHER REPRODUCTIVE EFFECTS

Wyrobek and London (1973) reported the appearance of abnormal sperm in mice receiving 0.1-0.9 of the methylhydrazine LD_{50} (not stated) for 5 days. Dose and dose-time related reversible abnormalities in the cauda epididymides and sperm morphology of mice were observed.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Methylhydrazine has been shown to impair renal and hepatic functions, cause convulsions, induce cholestasis, produce hemolytic anemia and increase blood methemoglobin concentration upon subchronic and chronic administration.

Darmer and MacEwen (1973) reported the effects of subchronic exposure to methylhydrazine vapor in three species. Groups of 8 female beagles, 4 female Rhesus monkeys and 80 male Sprague-Dawley rats were exposed to 0, 0.04 or 0.1 ppm methylhydrazine vapor continuously for 90 days. Body weights were recorded and blood evaluations were performed on samples obtained prior to exposure and at intervals during exposure.

No adverse effects were observed in any species exposed to 0.04 ppm or in monkeys at any exposure level. Decreases in hematocrit values, hemoglobin concentrations and erythrocyte counts were observed in rats and dogs exposed to 0.1 ppm methylhydrazine, but the only observations that had statistical significance when compared to controls were reduced body weight gain in rats and elevated serum phosphorus levels in dogs.

Haun (1971) investigated the toxic effects of subchronic methylhydrazine vapor exposure in four species. Groups of 8 female beagles, 4 female rhesus monkeys, 50 male Wistar rats and 40 female ICR mice were exposed to 0, 2 or 5 ppm methylhydrazine vapor 6 hours/day, 5 days/week for 26 weeks. Behavioral observation, body weights and hematological parameters were obtained and recorded biweekly. One rat was killed each month for histopathological evaluation. Lethargy was observed in mice exposed to 5 ppm, but not in any other species/concentration group. Dose-related decreases in hematocrit values, hemoglobin concentration and erythrocyte counts were observed in dogs and monkeys. Dogs showed a dose-response relationship in erythrocyte fragility and had serum bilirubin and alkaline phosphatase levels that were significantly different from controls. Splenic hemosiderosis was observed in exposed rats, and exposed dogs had black livers. Enlarged spleens were observed in mice exposed to 5 ppm, but not 2 ppm, methylhydrazine. These observations are consistent with the pattern of erythrocyte destruction and recycling of hemoglobin by the liver and spleen, which are thought to occur during methylhydrazine metabolism.

Attempting to evaluate chronic toxicity at the present TLV concentration, MacEwen and Haun (1971) repeated the previous experiment but added a lower methylhydrazine level, 0.2 ppm. Similar groups of animals were exposed to 0, 0.2, 1, 2 or 5 ppm methylhydrazine vapors 6 hours/day, 5

days/week for 6 months, or 0.2 ppm continuously for 6 months. Biweekly blood samples and weight measurements were taken from all exposed animals.

Reversible adverse effects on blood were observed in monkeys and dogs at all exposure levels. Hemolytic responses in dogs and monkeys exposed to 0.2 ppm continuously were not different from those exposed to 1 ppm intermittently. Hemolysis, decreased hemoglobin hematocrit and erythrocyte counts and formation of Heinz bodies were observed during exposure, and returned to normal 2-4 weeks after exposure. All exposed dogs had mean bilirubin, alkaline phosphatase and total inorganic serum phosphorus levels that were higher than controls.

Kroe (1971) performed histological analysis on tissue samples from the experimental animals used in the previous study (MacEwen and Haun, 1971). No lesions were found in monkeys or rats. Mice from all exposure groups had no lung or heart lesions attributed to methylhydrazine, but the livers, spleens and kidneys of mice exposed continuously or intermittently had evidence of hemosiderosis. Mice exposed to 2 and 5 ppm also had centrilobular cholestasis and bile duct proliferation. Dogs exposed to 5 ppm had periportal hepatic hemosiderosis and cholestasis and proximal tubular hemosiderosis. The morphology observed in dogs exposed to 2 ppm was similar, but distinguishable from the higher exposure level. No lesions were observed in the brains, lungs, hearts, spleens or endocrine glands of exposed dogs. Continuous exposure of dogs to 0.2 ppm and intermittent exposure to 0.2 or 1 ppm resulted in moderate lymphoid hyperplasia.

Species-specific response to the toxic effects of methylhydrazine is believed to arise from variable susceptibility to hemolysis and ability to clear the hemolysis products.

5.6. OTHER RELEVANT INFORMATION

Much data regarding the acute toxicity of methylhydrazine are available. As reviewed by NIOSH (1978) some effects of acute methylhydrazine intoxication include death, hemolysis, convulsions, irritation, methemoglobin formation and renal and hepatic damage. Acute LC_{50} values for inhalation range from 74 ppm (rats exposed for 4 hours) to 390 ppm (dogs exposed for 15 minutes). Oral LD_{50} values of 71 mg/kg for rats and 22 mg/kg for hamsters have been reported. Dermal LD_{50} values range from 47 mg/kg for guinea pigs to 183 mg/kg for rats.

To evaluate the adequacy of the methylhydrazine 10-minute emergency exposure limit (EEL) of 90 ppm, MacEwen et al. (1971) exposed 7 male volunteers to this concentration for 10 minutes. Subjects were monitored for 60 days after exposure. Lacrymation, eye redness and nasal irritation were generally observed, and the only abnormal hematologic parameter observed was a slight, reversible increase in Heinz body formation. The authors concluded that the present EEL was acceptable.

Smith and Clark (1969) observed methemoglobin formation, increased production of bile pigment and renal damage in dogs administered methylhydrazine percutaneously. The authors surmised that renal damage may be caused by the increased bile pigment from hemolysis. The autoxidation of methylhydrazine to hydrogen peroxide and the inhibition of catalase were thought to contribute to methemoglobin production. The delay between the administration of methylhydrazine and methemoglobin detection in blood appeared to be compatible with a mechanism of methemoglobin formation based on the inhibition of catalase.

The *in vitro* production of methemoglobin in methylhydrazine exposed erythrocytes has been reported in blood samples from humans (Fortney and Clark, 1967; George, 1973) and other species (Leahy, 1970).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The acute toxicity of methylhydrazine was determined for the guppy, Poecilia reticulata, in static (aerated) tests using hard and soft water (Slonim, 1977). In hard water (400-500 mg $CaCO_3$/ℓ) the 24-, 48-, 72- and 96-hour LC_{50} values of 5.26, 4.02, 3.67 and 3.26 mg/ℓ, respectively, were determined. Methylhydrazine in soft water (20-25 mg $CaCO_3$/ℓ) was similarly toxic, having 24-, 48-, 72- and 96-hour LC_{50} values of 6.69, 3.66, 2.74 and 2.58, respectively (Slonim, 1977). Klein and Jenkins (1977) reported that the 24-hour LC_{50} for guppies exposed to methylhydrazine ranged from 2.6-6.7 mg/ℓ. In the golden shiner, Notemigonus crysoleucas, the 96-hour LC_{50} was reported to be 2.27 mg/ℓ when tested in water of moderate hardness (140-172.8 mg/ℓ) (Fisher et al., 1980). The channel catfish, Ictalurus punctatus, was slightly more tolerant than the guppy or the golden shiner, having a 96-hour LC_{50} of 3.54 mg methylhydrazine/ℓ (Fisher et al., 1980).

The toxicity of methylhydrazine was also tested in two crustaceans (an isopod and an amphipod). The amphipod, Hyalella azteca, had a 48-hour LC_{50} value of 1.2 mg/ℓ, while the isopod was slightly more sensitive to methylhydrazine with a 48-hour LC_{50} of 0.82 mg/ℓ (Fisher et al., 1980).

6.2. CHRONIC TOXICITY

The embryo-larval toxicity and teratogenicity of methylhydrazine was tested in the South African clawed toad, Xenopus laevis (Greenhouse, 1976a,b). Embryos exposed at 0, 3, 5, 10 and 15 mg methylhydrazine/ℓ developed malformations in 3, 1, 52, 93 and 100% of the cases. Malformations included kinked tail, trunkated body and notochordal abnormalities (Greenhouse, 1976a). The survival of X. laevis tadpoles (larvae) was

tested with exposure to 0.01, 0.1, 1.0, 2.0 and 5.0 mg/ℓ. Survival after 120 hours was 100, 100, 0, 0 and 0% of the exposed larvae (n = 50 or 110/dose group). Tadpoles exposed to 0.1 mg/ℓ continuously during maturation proceeded through metamorphosis normally (Greenhouse, 1976b).

6.3. PLANT EFFECTS

The EC_{50} for reduced cell growth in algal bioassays (species not determined) was ~7.0 mg/ℓ (Scherfig et al., 1977). Additional data regarding the effects of methylhydrazine exposure in aquatic plants were not located in the available literature.

6.4. RESIDUES

Data regarding methylhydrazine residues in aquatic organisms were not located in the available literature. However, since methylhydrazine is miscible with water and since log BCF is inversely related to the log of water solubility, methylhydrazine is not likely to bioaccumulate significantly in aquatic organisms.

6.5. OTHER AVAILABLE INFORMATION

Additional information pertinent to the aquatic toxicity of methylhydrazine was not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The American Conference of Governmental Industrial Hygienists recommend a 0.2 ppm ceiling limit for methylhydrazine and designate it A-2, a suspected carcinogen (ACGIH, 1980).

The National Institute of Occupational Safety and Health recommends that methylhydrazine exposure be controlled to 0.04 ppm (NIOSH, 1978).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of methylhydrazine were not located in the available literature.

8. RISK ASSESSMENT

Upon review of the available data, it is evident that methylhydrazine is a toxic compound with some potential to induce cancer in hamsters and mutations in bacterial systems. Methylhydrazines hemolytic effects and subsequent liver, spleen and kidney damage are less sensitive endpoints than the carcinogenicity observed in hamsters (Toth and Shimizu, 1973) upon oral administration.

While there are few substantiating data from other sources, the increased incidence of malignant liver histocytoma (27/50 treated, 0/50 controls) observed in male hamsters can provide a basis for estimating the carcinogenic risk of methylhydrazine to humans.

Treated male hamsters ingested from their drinking water an average of 1.1 mg methylhydrazine/day for their lifetimes. The transformed dose of 9.2 mg/kg/day is obtained by dividing the daily dose by the assumed weight of the hamsters (0.12 kg). Based on this data from Toth and Shimizu (1973) and using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a q_1^* of 1.09 $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose associated with an increased lifetime risk of 10^{-5} is 9.17×10^{-6} mg/kg/day, or 6.42×10^{-4} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix B.

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APPENDIX A
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: Methylhydrazine

Reference: Toth and Shimizu, 1972

Species, Strain, Sex: Hamsters, Syrian golden, male

Body Weight: 0.12 kg (assumed)

Length of Exposure (l_e) = 700 days

Length of Experiment (L_e) = 700 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: Liver, malignant histiocytomas (Kuppfer's cell sarcoma)

Route, Vehicle: Oral, drinking water

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/ No. Tested (or examined)
0	0	0/50
1.1 mg/day	9.2	27/50

Human $q_1^* = 1.09\ (mg/kg/day)^{-1}$

10^{-5} risk level = 9.17×10^{-6} mg/kg/day, 6.42×10^{-4} for 70 kg man